Remarks

Claims 1 to 5 and 12 to 19 are withdrawn from further consideration. Claims 20 to 26 have been examined and the elected species of SEQ ID NO:1 has been searched. Claim 27 to 31 have been added and are supported, e.g., by the original claims (see also Office Action, paragraph 15).

Specification

On page 3, the Office objected to the disclosure considering the title as being not descriptive and the abstract being longer than a paragraph.

In response, the title was amended to "Peptides of the AT_1 Receptor and their Uses" and the abstract was combined into a paragraph.

Claim Objections

Also on page 3, the Office objected to claim 20 because "A_1" should read "AT_1."

In response, applicants amended the claim accordingly.

Claim Rejections – 35 USC §112,2nd paragraph

On pages 3 and 4, paragraphs 9 to 13 of the Action, the Office rejected claims 20 to 26 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office based the indefiniteness rejection on the phrases "contacting said peptides with a body fluid" stating that it is unclear whether the limitation refers to a body fluid from a patient suspected of having preeclampsia. The Office also rejected the phrase "binding said auto-antibodies in said body fluid via said peptides" stating that it is unclear what additional method steps are intended.

In response to the first part of the rejection, applicants have amended the phrase "contacting said peptides with a body fluid" to "contacting said peptides with a body fluid

from a patient suspected of having preeclampsia or malign hypertension" to clarify the claim as indicated by the Office.

In response to the second part of the rejection, applicants have expanded on the phrase "binding said auto-antibodies in said body fluid via said peptides" to clarify what additional method steps are intended. Support for this amendment can be found in the abstract; on page 6, the penultimate paragraph, which starts on line 23; on the first paragraph on page 1, which starts on line 3 and the example on page 8, second paragraph starting on line 9.

Claim Rejections – 35 USC §112,1st paragraph (enablement)

Starting on page 4, paragraphs 14 to 23, the Office rejected claims 20-26 under 35 USC §112, first paragraph, stating that the specification does not enable the person skilled in the art to which it pertains, or with which it most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The Office acknowledged that the specification is enabling for

(1) a method for detecting auto-antibodies against the angiotensin AT_1 receptor in a body fluid comprising
contacting an isolated peptide of peptide of the AT_1 receptor with a body fluid under conditions permitting binding of said auto-antibodies with said peptide, wherein the peptide consists essentially of the amino acid of SEQ ID No. 1 and wherein the body fluid is maternal blood; or
(2) a method of binding auto-antibodies against the angiotensin AT_1 receptor in a body fluid *in vitro* comprising
contacting an isolated peptide of the AT_1 receptor with a body fluid under conditions permitting binding of said auto-antibodies with said peptide, wherein the peptide consists essentially of the amino acid sequence of SEQ ID No 1, and wherein the body fluid is maternal blood.

However, the Office expressed the opinion that the specification is not enabling for the invention as claimed, taking in particular note of the reference to peptides comprises 5 to 30 amino acids of the AT_1 receptor, any in vivo contact with the body fluid and the body fluid being something other than maternal blood.
In its determination as to whether any necessary experimentation is undue, the Office considered the "Wands factors", including, but not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The Office stated that while the specification teaches that the peptide consisting of SEQ ID NO:1 is able to bind and inhibit the effect of auto-antibodies against the angiotensin AT_1 receptor (see pg 7, Figure 2), it does not teach a commensurate number of peptides that are encompassed by the scope of the claims that also exhibit these activities. The Office in particular expressed the opinion that while the specification teaches that the peptide consisting of SEQ ID NO:1 is able to bind and inhibit the effect of auto-antibodies against the angiotensin AT_1 receptor (see pg 7, Figure 2), the specification also teaches that the agonistic effect of the autoantibodies achieved via the AT_1 receptor was only neutralized by the peptide consisting of the amino acid sequence of SEQ ID NO:1 (See pg 8). Furthermore, the specification also teaches that SEQ ID NO:1 (an epitope on the second extracellular loop of the AT_1 receptor, has a special importance in preeclampsia, since it was identified an all of the patients examined (See pg 8)).

Applicants respectfully submit that in the example of Figure 2 the effects of a number of peptide sequences on the AT_1 receptor are described. In the set-up provided, only SEQ ID NO:1 was able to inhibit the effect of the auto-antibodies. Example 3 on page 8 describes a bioassay for the detection of antibodies of 2

patients. Applicants note that the results are not more than examples that demonstrate the binding properties of the different peptides. Notably, the example 3 discusses that the peptides ENTNIT and AFHYESQ were able to neutralize the antibodies in hypertension sufferers. The last sentence of Example 3 clarifies that functional analog peptides SHFYQTR and GYYFDTN are also able to neutralize the antibodies. This sentence is not limited to the peeclampsia patients mentioned in the previous sentence. As functional analog peptides that were, as discussed above, also tested in hypertension sufferers, these functional analogs can equally be expected to work in malign hypertension. The fact that the example does not show results for ENTNIT in preeclampsia patients does not mean that this peptide is not able to neutralize the antibody. The example is specific and only examined two patient samples using an antibody dilution of 1:40. Knowing that, e.g., different antibody dilutions, different peptide concentration and incubation times might very well provide different results, the person skilled in the art would not draw negative conclusions from this specific example (in fact, ENTNIT turned out to be effective in preenclampsia patients at higher concentrations).

The Office also expressed the opinion that the relationship between the sequence of a protein and its activity is not well understood and unpredictable, and that certain positions in the sequence are critical to the protein's structure/function relationship and can only tolerate relatively conservative substitutions or no substitutions. While the Office acknowledged that it is known that many amino acid substitutions are generally possible in any given protein, the Office expressed the opinion that the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited.

The Office concluded that due to the large quantity of experimentation necessary to generate the infinite number of variants and derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the

specification regarding which structural features are required in order to provide activity, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

In response, applicants have amended claim 20 to recite that the 5 to 20 amino acids are of loop II of the receptor or are functional analogs thereof. The amendment is supported by page 3, e.g., the third full paragraph, starting on line 13 and, e.g., the description of Figure 2 on page 7 of the specification. Thus, the sequences are now limited to a specific loop of the AT_1 receptor, namely loop II, thus substantially reducing any experimentation that might be required. Applicants also have shown that specific functional analogs do provide positive results (see, e.g., Table 1 on page 8).

Applicants respectfully submit that the person skilled in the art knew how to perform and the specification teaches an epitope analysis of the loop II sequences (see Fig. 2). At the time the invention was made, it was also well known in the art how to produce functional analogs. Applicants would like to refer the Office to the article of Schneider et al., Proc. Natl. Acad. Sci, USA Vol. 95, pp 121979 -84 (1998) as referenced in the IDS submitted to the Office on September 20, 2007.

Applicants also submit (and the Office seemed to concede) that it is known to a person skilled in the art that individual amino acids demonstrate analogous physicochemical properties, which advantageously lead to the result that these amino acids can be substituted for one another. These include, for example, the group of amino acids (a) glycine, alanine, valine, leucine, and/or isoleucine; or the amino acids (b) serine and threonine; the amino acids (c) asparagines and glutamine; the amino acids (d) asparaginic acid and glutaminic acid; the amino acids (e) lysine and arginine; as well as the group of aromatic amino acids (f) phenyl alanine, tyrosine, and/or

tryptophan. Amino acids within one and the same group (a-f) can be replaced for one another. Applicants also refer to WO99/62933, which discusses possible modifications.

Thus, considering the limited breadth of the claims (Wands factor 6 above), the state of the prior art and the relative skill of those in the art as outlined above (Wands factors 2 and 3 above), respectively, applicants submit the guidance provided in the specification is such that no undue experimentation is needed to make and/or use the invention commensurate with the scope of the current claims.

The Office acknowledged that the specification provides adequate direction and guidance on how to bind or detect auto-antibodies against the AT_1 receptor in a body fluid, i.e., maternal blood, *in vitro*. However, the Office expressed the opinion that there is no guidance on how to bind said auto-antibodies in the body fluid *in vivo*. The Office also expressed the opinion that one skilled in the art would not know, with any level of predictability, that the administration of an undetermined amount of the peptide of SEQ ID NO:1 would be able to bind auto-antibodies of the AT_1 receptor *in vivo*. In particular, the Office argued that the state of the prior art establishes the unpredictability of delivering proteins to a subject. In the absence of this guidance, the Office argues, a practitioner would have to resort to a substantial amount of undue experimentation involving the variation in the amount and duration of administration of the peptide of SEQ ID NO: 1, and making a determination of whether a successful result was achieved.

Applicants submit that if binding of a peptide to a certain antibody has been established, the person skilled in the art knows how to bind the antibody to the peptide not only *in vitro*, but also *in vivo*.

Applicants submit that the person skilled in the art could, e.g., bring the peptides into the blood stream of a patient for binding. The binding could be subsequently detected for diagnostic purposes. Such a binding would also result in the neutralization of the auto-antibody as set forth in the claims after, e.g., the peptides are injected. The

correlation that the MPEP calls for in section §2164.02 refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. Applicants submit that for the invention as claimed the appropriate correlation to the data set forth in the application is provided.

Applicants also note that the scope of enablement clearly reaches beyond maternal blood as a body fluid. Applicants submit that malign hypertension is not a disease limited to expectant mothers and respectfully refers to the example disclosed on page 8 of the application, which supports that the epitopes ENTNIT and AFHESQ peptides annulled the effect of the antibody in hypertension suffers. The specification also explicitly states on page 6 that the examples of preeclampsia can be equally used for some cases of malign hypertension in which an autoantibody recognizing the same epitope (the same sequence) is found. The Office has not formulated any arguments that would undermine the veracity of this statement (penultimate paragraph of page 6). As set forth in §2164.04 of the MPEP referring to *In re Marzocchi,* "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

Claim Rejections – 35 USC §112, 1st paragraph (written description)

Starting on page 10, paragraphs 24 to 30, the Office rejected claims 20, 21, and 24-26 under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The Office expressed the opinion that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention.

The Office acknowledged that the specification provides an adequate written description for an polypeptide consisting of the amino acid sequence SEQ ID NO:1 that binds and inhibit the effect of autoantibodies against the angiotensin AT_1 receptor, the Office

expressed the opinion that it does not provide an adequate written description for a commensurate number of the claimed species of peptides that also bind and inhibit the effect of autoantibodies against the AT receptor.

Applicants have amended claim 1 to limit the sequences to 5 to 30 amino acids of loop II of the AT_1 receptor (compare sequences disclosed in Fig. 2 that belong to loop II).

As the Office noted, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. (MPEP §2163)

Factors to be considered in determining whether there is sufficient evidence of possession include: (1) the level of skill and knowledge in the art, (2) partial structure, (3) physical and/or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and (5) the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. (MPEP §2163)

Structures of the loop II have been provided and their physical properties have been discussed (See Fig. 2) (see factors (2) and (3)). As noted in the context of the enablement rejection, the specification in fact provides examples directed to two loop II sequences and two function analogs. The level of skill and knowledge in the art (1) was discussed above with reference to the teachings of Schneider et al., which describes ways to produce function analogs at the time the invention was made. Methods of making the claimed invention are also disclosed (5).

Thus, applicants submit that a written description commensurate with the scope of the invention as currently claimed has been provided.

The Commissioner is authorized to charge or credit undersign's deposit account 50-3135 for any payments that may become due with this response.

Respectfully submitted,

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